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TRANSMITTAL FORM

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Application Number	10/050,121
Filing Date	January 18, 2002
First Named Inventor	Randolph M. Howes
Art Unit	1616
Examiner Name	Frank I Choi
Attorney Docket Number	29794/04001

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☑ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation
- ☐ Change of Correspondence Address
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- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☑ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☑ Other Enclosure(s) (please Identify below):

Remarks

Return receipt postcard
Four (4) Appendices (108 pages)

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

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Date	June 10, 2005	Reg. No.	42,920

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	)	
	)	
Randolph Howes	)	Group Art Unit: 1616
	)	
Application No.: 10/050,121	)	Examiner: Frank I. Choi
	)	
Filed: January 18, 2002	)	Attorney Docket No.: 29794/04001
	)	
For: Compositions, Methods, Apparatuses and Systems for Singlet Oxygen Delivery	)	

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Commissioner for Patents
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APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Further to the Notice of Appeal filed February 21, 2005, this Appeal Brief is responsive to the non-final Office Action mailed December 30, 2004. This Appeal Brief is also responsive to the Notice of Non-Compliant Appeal Brief, mailed May 13, 2005.

I. Real Party In Interest

The inventor, Randolph M. Howes, is the real party in interest.

II. Related Appeals and Interferences

To the knowledge of Appellant or his representative, there are no other appeals or interferences that will directly affect, be directly affected by, or have a bearing on the Board's decision in this appeal.

III. Status of Claims

Claim 1-12 and 14-46 are pending in this application. The Office withdrew claims 5, 11, 17-28, and 30-46, as directed to a non-elected invention. Appellant previously canceled claim 13. The Office rejected claims 1-4, 6-10, 12, 14-16, and 29.

Appellant appeals the rejection of claims 10, 16, and 29.

IV. Status of Amendments

Appellant submits concurrently herewith an Amendment, which reduces issues for this Appeal. The Amendment incorporates the limitations of independent claim 1 into claim 10, and of independent claim 14 into claim 16. Other claims are canceled, leaving claims 10, 16, and 29 pending.

V. Summary of Invention

The invention relates to methods of treating a tumor in or on a mammal, comprising: administering at least one source of peroxide and at least one source of hypochlorite anion to the tumor to be treated, wherein the at least one source of peroxide and at least one source of hypochlorite are from separate sources, and allowing the peroxide and hypochlorite to react to produce singlet oxygen at the tumor or during administration. (Claim 10; see, for example, page 11, paragraph [030].)

Other aspects of the invention include systems for treating a tumor, in a mammal, comprising: a) at least one source of peroxide; b) at least one source of hypochlorite anion, which is separate from the source of peroxide; and c) at least one catheter having at least one

lumen. (Claim 16; see pages 39-40, paragraphs [0123] through [0129].) In another aspect, the invention relates to methods for treating tumor cells or cancer cells as a result of seeding an operative site comprising: administering as an irrigation or irrigating solution at least one source of peroxide and at least one source of hypochlorite anion. (Claim 29; see page 48, paragraph [0148].)

Appellant recognized that sodium hypochlorite and hydrogen peroxide are toxic, and potentially harmful, if delivered alone. While these agents could be useful for treating abnormal cells, each could be predicted to have undesirable collateral effects on adjacent, normal cells. Appellant further recognized that when combined, hypochlorite and peroxide react to form singlet oxygen and the relatively harmless by-products, sodium chloride and water. Singlet oxygen itself exhibits a powerful oxidizing effect, but is short-lived. Appellant theorized that singlet oxygen could be a useful agent for treating abnormal cells when delivered through the combination of hypochlorite and peroxide.

A working example (Example 1; pages 50-52) describes one specific embodiment within the scope of some of the appealed claims. Briefly, a keratotic lesion is treated by sequential administration of sodium hypochlorite and hydrogen peroxide. The results of the process are presented. (Figures 12-18.)

Through this initial test of the invention, Appellant confirmed that which would have been unexpected in the art, namely that treatment by administration of hypochlorite and peroxide could produce beneficial results with minimal collateral damage. Surprisingly, Appellant observed another unexpected effect: the collateral damage that did occur (if any) appeared to be reversible within a short period of time after treatment. Thus, while abnormal cells were oxidized, died, and did not re-grow, normal cells that were collaterally affected recovered and filled the space previously occupied by abnormal cells. (See Example 1, pages 50-52.) These results were certainly unexpected and could not have been predicted. Similar results were observed in additional treatments of skin keratoses, the results of which are described in Appellant's continuing application (U.S. Patent Application No. 10/331,773, a copy of which is attached; see Example 2, pages 89-92).

These unexpected results were also observed in tumor treatment. A prophetic example is set forth in Appellant's specification in Example 6 (page 55). A working example performed in a mouse tumor model is shown in the aforementioned continuing application (Example 13, pages 103-107). Promising results were also observed in equine carcinoma (Examples 6 and 7 of the continuing application), but the horse ultimately died from its already advanced metastasis. It should be noted that these examples merely demonstrate the invention described in the present application.

VI. Issues

A) Whether claims 10, 16, and 29 are obvious over Ameta et al. (*Asian Journal of Chemistry Reviews*, 1(2):106-124 (1990)), in view of "the acknowledged prior art," Colic (U.S. Patent No. 6,544,401), and Beattie et al. (U.S. Patent No. 5,364,344).

B) Whether claims 10, 16, and 29 are obvious over Rosen et al. (Journal of Biological Chemistry (1977) Vol. 252 (No. 14): 4803-4810) in view of the "acknowledged prior art," Vincent et al. (Cancer (1964) 17: 997-1005), Mallams et al. (Prog. Clin. Cancer (1965) Vol. 10: 137-153), and Beattie et al. (U.S. Patent No. 5,364,344).

VII. Grouping of Claims

The appealed claims stand or fall together.

VIII. Argument

A) Claims 10, 16, and 29 are not obvious over Ameta et al. (*Asian Journal of Chemistry Reviews*, 1(2):106-124 (1990)), in view of "the acknowledged prior art," Colic (U.S. Patent No. 6,544,401), and Beattie et al. (U.S. Patent No. 5,364,344).

Claim 10 is exemplary of the rejected claims. Claim 10 (including the elements of claim 1) is directed to: "A method of treating a target site in or on a mammal, comprising: administering at least one source of peroxide and at least one source of hypochlorite anion to the

target site to be treated, wherein the at least one source of peroxide and at least one source of hypochlorite are from separate sources, and allowing the peroxide and hypochlorite to react to produce singlet oxygen at the target site or during administration, wherein the target site is a tumor."

The Differences Between the Claims on Appeal and the Prior Art

Appellant's claim requires *administration* of *at least one source of peroxide* and *at least one source of hypochlorite* to *allow for the generation of singlet oxygen* at the tumor. The prior art fails to teach the administration of hypochlorite and the administration of peroxide, in combination, to produce singlet oxygen at a target site.

The Cited Prior Art

Colic

Applicant notes that Colic issued as a U.S. Patent after Applicant's effective filing date but was filed April 28, 2000 and claims priority to a provisional patent application filed April 29, 1999. Applicant invented the claimed subject matter before the effective date of Colic, as demonstrated by the Declaration under 37 C.F.R. § 1.131, previously filed in this application.[1] Thus, Colic is not available as a reference against the claimed invention.

Turning to the Office's treatment of the previously filed Affidavit under 37 C.F.R. § 1.131, Applicant respectfully notes that the claims have been amended to recite that the "target site" is "tumor." Applicant respectfully submits that the presently claimed treating of a tumor would have been an obvious modification of the species completed by Applicant in the reduction to practice of treating the dermal nevus and keratosis, which is described in the Affidavit. Thus, by amending the claims, Applicant has removed the genus-species issue raised by the Office.

The Office's reliance on 37 C.F.R. § 1.601 with regard to the Affidavit is misplaced. Section 601 relates to interference practice, as its preamble clearly states: "1.601 Scope of rules,

[1] Applicants submit herewith a copy of the Affidavit under 37 C.F.R. § 1.131 previously filed in this application.

definitions. This subpart governs the procedure in patent interferences in the Patent and Trademark Office." The same can be said for the reference to section 601 in M.P.E.P. 706.02(b). In this instance, the Office's attention is respectfully directed to M.P.E.P. 2138.01, where it is explained that interference practice operates to the exclusion of *ex parte* practice under 37 C.F.R. § 1.131. The obvious reason for this exclusion is that if the two patents claim the "same patentable invention," then the appropriate forum for deciding patentability is an interference proceeding -- not *ex parte* patent examination. In this instance, Applicant respectfully submits that the claims do not constitute the "same patentable invention" as defined in 36 C.F.R. § 1.601(n).

Thus, Applicant respectfully submits that the previously filed Affidavit is sufficient to antedate Colic.

Appellant's Argument

Applicant submits that the rejection is untenable as presented, and is even more untenable in the absence of Colic, which Applicant has antedated. Because the Office's rejection over a combination of references included Colic, Applicant will treat the cited documents individually.

The Office relies on Ameta et al., which is alleged to disclose that "singlet oxygen can be prepared by photosensitization in which oxygen is passed into a solution containing a dye and a substrate exposed to visible or u.v. light or by the reaction between sodium hypochlorite and hydrogen peroxide in which the other products are NaCl and water." The photosensitization reaction described by Ameta et al. is at the heart of photodynamic therapy, which Applicant has described in the Background section of the application (see, for example, paragraphs [009]-[016]). The reaction between sodium hypochlorite and hydrogen peroxide to yield singlet oxygen, with water and sodium chloride as by-products, was described by Foote and Wexler in 1964 (see, for example, paragraphs [017] and [018] of the specification).

The Office asserts that Applicant acknowledges that singlet oxygen is effective against tumor cells and cancer (citing paragraph [009], which relates to photodynamic therapy, referred to above), but that there are drawbacks of those methods (citing paragraphs [013]-[015], which

describe the drawbacks of photodynamic therapy, also referred to above). The Office states that Applicant discloses that the singlet oxygen produced by photodynamic therapy is identical to that produced by hypochlorite and peroxide (citing paragraph [017], also referred to above). The Office asserts that Applicant acknowledges that singlet oxygen is an oxidizing component of human neutrophils (citing paragraph [019]). Finally, the Office asserts that Applicant acknowledges that singlet oxygen is short-lived (citing paragraph [084]).

The Office cites Colic, but as noted above, Colic has been antedated and its disclosure is now irrelevant. The Office cites Beattie et al. as teaching a dual lumen catheter, which can be used for delivering different fluids into a bloodstream.

In the absence of Colic, the question is whether the claimed invention is obvious over Ameta et al. in view of the "acknowledged" prior art and Beattie et al. Applicant respectfully maintains that the claimed invention is not obvious.

The Office rejects the pending claims over Ameta et al. in view of "acknowledged prior art" and Beattie et al. The Office refers to alleged acknowledged prior art that relates to 1) photodynamic therapy and the attendant production of singlet oxygen by photo-oxidation of dye compounds (referring to paragraphs [009], [013], [014], and [015]), and 2) other background information relating to singlet oxygen, such as the fact that it can be made by a hypochlorite-peroxide reaction, that it is short-lived, and that it is found in human neutrophils.

Ameta et al.

This document is a review article relating to the chemistry of singlet oxygen. It notes that singlet oxygen can be produced in a variety of ways, including physical methods such as photosensitization, and chemical methods such as by reacting sodium hypochlorite with

hydrogen peroxide. Ameta et al. also describes the lifetime of singlet oxygen in various solvents, including water, in which the lifetime is on the order of microseconds.[2]

But what Ameta et al. also clearly states, and what the Office fails to note, is that singlet oxygen is also released from the solid adducts formed in reaction between triaryl phosphite and ozone at low temperature, that it is a decomposition product of superoxide, that peroxyacetyl nitrates decompose in the presence of alkali to give singlet oxygen, that organic peracids decompose in alkaline solutions to produce singlet oxygen, and that singlet oxygen is generated by the adsorption and decomposition of ozone on silica gel. And beyond the chemical methods, Ameta et al. states that singlet oxygen can be created by electrodeless microwave or radiofrequency discharge in an oxygen environment.

While the Office cites Ameta et al. for the discussion of producing singlet oxygen by photosensitization or by the hypochlorite-peroxide reaction, in fact, the authors give no more attention to the reaction of hypochlorite and peroxide to produce singlet oxygen than they do to any other topic. When one reads the entire document, one sees that the authors spend at least two pages discussing the *photodynamic effects* of some organic compounds. (See Ameta et al., pages 117 and 118.) They state that the discovery that microorganisms are killed by light in the presence of oxygen and a sensitizing dye is called "photodynamic action" and includes cell damage, induction of mutations or cancer, and ultimate death. They point out that these "effects *are due to photo-oxidation* of various sensitive cell constituents." (*Id.*, page 117.)

While Ameta et al.'s discussion is generally related to the chemistry of singlet oxygen, to the extent that it does extend to biological applications of that chemistry, those discussions relate to photochemical reactions and photodynamic effects. If Ameta et al. can be said to suggest any biological application, it is photodynamic therapy.

In response to Applicant's argument that the Office has focused on one particular method without any reason, the Office suggests that one "would choose the H_2O_2/hypochlorite process as

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[2] Applicant notes that the specification suggests (at paragraph [084], for example) that singlet oxygen lifetime is an order of magnitude less, i.e., nanoseconds. This difference is not believed to impact any determination of patentability and is believed to result from differing published reports on the lifetime value.

it is a common method of forming singlet oxygen and singlet oxygen is effective in treating tumors." (Office Action, page 6, lines 5-6.) The Office cites the Supreme Court case of *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327 (1945) in support of its position. Applicant respectfully submits that *Sinclair* does not support the Office's position.

Sinclair involved a patent related to rapidly drying printing ink. All that was needed for such an ink was a solvent that evaporated quickly upon heating. The inventor, knowing that a rapidly drying printing ink was needed, and further knowing that all that was necessary to produce such an ink was a solvent that would evaporate on heating, simply chose a known solvent that exhibited those characteristics from a list of known solvents. The solvent chosen imparted nothing else to the composition except its own known characteristic of evaporation upon heating. The Court found that this was akin to selecting the last piece of a jigsaw puzzle. *Sinclair* at 335.

Importantly, the solvent in *Sinclair* bore no functional relationship to the ink, and it served only as an inert carrier. The choice of solvent was dictated by known, *required* properties of the end product. *U.S. v. Adams*, 383 U.S. 39, 50 (1966). Once the inventor was told exactly what qualities were needed for the ink, he simply selected the desired solvent from a catalog list of solvents that showed their boiling points and vapor pressures.

As discussed above, Ameta et al. discusses a number of methods for producing singlet oxygen. Only one of those methods, photo-oxidation, is discussed in the context of a cytotoxic effect, or in the context of any clinical utility. Thus, if a person of ordinary skill in the art was charged with reading Ameta et al. and selecting from its "list" an appropriate method for treating cancer (i.e., making a choice based on the known properties of that choice; e.g., selecting a solvent based on its boiling point), one would choose photo-oxidation, because that is the one method that is discussed in the context of treating cancer. One would not choose the hypochlorite/peroxide system (as *Sinclair*'s inventor would not have chosen a solvent for which the boiling point was unknown).

"Acknowledged" Prior Art

The Office cites to several paragraphs from Applicant's application that discuss photodynamic therapy in animals. Photodynamic therapy generally involves infusing a photoactive compound into a patient and allowing the compound to collect in a tumor that is to be targeted. The photoactive compound in the tumor is then irradiated with light energy to produce singlet oxygen in the target site. There are drawbacks to photodynamic therapy, which include targeting problems as well as expense. But photodynamic therapy does not involve, or relate to the use of, either peroxide or hypochlorite.

The Office cites to paragraph [017] of Applicant's specification for the proposition that the singlet oxygen made by photodynamic therapy is identical to that produced by reacting hypochlorite with peroxide. But that fact does not lead from one method of production to the other. As noted to Ameta et al., there are at least six chemical methods for making singlet oxygen, any of which would appear equally attractive. There is no reason a person skilled in the art would choose any particular method. And, as noted above, when Ameta et al. discusses singlet oxygen in the context of biological applications, it discusses photodynamic therapy.

The Office also cites to Applicant's application (paragraph [019]) for the premise that singlet oxygen is recognized as being naturally present in humans. Applicant's discussion in this section of the application simply describes what was believed to be current hypotheses on the functioning of eukaryotic cells. These cells are believed to produce, through complicated enzymatic processes, hydrogen peroxide, hypochlorite, singlet oxygen, and other potent oxidizing compounds in connection with phagocytic activities. But this understanding of basic cell biology does nothing to teach or suggest Applicant's claimed invention.

U.S. Patent No. 5,364,344 to Beattie et al.

The Office cites to Beattie et al. for teaching dual lumen catheters for delivering different fluids into the bloodstream.

Applicant maintains that the teaching of Beattie et al. no more suggests the present invention than it does administering vinegar and baking soda for an effervescent effect. There is nothing in Beattie et al. that suggests any particular compounds or substances for administration.

Beattie et al. simply provides a means for administering two solutions simultaneously, *if one wanted to do so*. But given the art, there is no reason that one would want to administer at least one source of peroxide and at least one source of hypochlorite.

In the Office Action, the Office states that "one of ordinary skill in the art would expect that by use of a dual lumen catheter the peroxide and hypochlorite could be kept separate until the last possible moment thereby ensuring the maximum concentration of singlet oxygen possible." (Office Action, page 3, lines 17-19.) Applicant respectfully submits that none of the art relied upon by the Office suggests that peroxide and hypochlorite should be administered together for treating a mammal. Thus, it is irrelevant that one *could* use a dual lumen catheter. And the suggestion that one would use such a catheter to ensure "the maximum concentration of singlet oxygen possible" is completely unsupported.

Applicant's Argument

Obvious to Try is Not the Proper Standard

Applicant's claimed invention stems from the discovery that while toxic and potentially harmful if delivered alone, hypochlorite and peroxide can be delivered to react to form singlet oxygen. Singlet oxygen exhibits a powerful oxidizing effect, but is short-lived. The reaction products of sodium hypochlorite and hydrogen peroxide *in vivo*, thus, are short-lived singlet oxygen, sodium chloride, and water. When administered in this manner, the effect is specific to the local area, with little possibility for collateral damage. Indeed, Applicant has observed that what collateral damage does occur to normal cells is quickly reversed. While the oxidative effects are permanent on abnormal cells, the normal cells in the area are able to reproduce and heal the treated area. This surprising effect could not have been predicted, and would not have been expected given the prior art teachings.

Applicant's claims require the administration of hypochlorite *and* peroxide. Prior to Applicant's invention no one had ever simultaneously or sequentially injected peroxide and hypochlorite into a living animal, not to mention with the desired effect of producing singlet oxygen, and not to mention with the desired outcome of killing cancer cells. While it was known

that hypochlorite and peroxide would react to form singlet oxygen *in vitro*, no one knew or suggested that it could or should be done *in vivo*. Indeed, prior to Applicant's actual reduction to practice, it could not possibly have been known what the actual result would be. One could not have predicted that a desirable effect would be achieved.

Nevertheless, the Office asserts that the claimed invention is obvious. It asserts, based on the known *in vitro* reaction between hypochlorite and peroxide to produce singlet oxygen, the natural existence of short-lived singlet oxygen in humans, and the understanding that singlet oxygen is the active agent in photodynamic therapy of tumors, that it would have been obvious to treat a tumor by administering hypochlorite and peroxide. What the Office is suggesting here is that it would have been obvious to try: obvious to experiment with the reactants, hoping that a desirable outcome would be achieved, or obvious to test what would happen if the reactants were administered. But obvious-to-try is not the standard for determining whether an invention would have been obvious and the Federal Circuit has repeatedly warned against it.

A Simple Invention

As discussed in the application, photodynamic therapy involves administering a photoreactive dye compound, so that the compound is localized in the area to be treated, and selectively exposing the area to light, so that the photoreactive dye produces singlet oxygen. Applicant's invention also produces singlet oxygen at a target site, but does so much more simply: the compounds react to produce singlet oxygen at the target site without the need for photons to initiate the reaction. As compared to other methods, Applicant's invention is relatively simple.

Because of the simplicity of Applicant's invention, special care should be exercised to avoid an improper hindsight approach. "When the art in question is relatively simple, . . . the opportunity to judge by hindsight is particularly tempting. Consequently, the tests of whether to combine references need to be applied rigorously." McGinley v. Franklin Sports, Inc. 262 F.3d 1339, 1351, 60 U.S.P.Q.2d 1001 (Fed. Cir. 2001). *See in re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313 (Fed. Cir. 2000) ("With this simple concept in mind, the Patent and Trademark Office found prior art statements that in the abstract appeared to suggest the claimed limitation.

But, there was no finding as to the specific understanding or principle within the knowledge of a skilled artisan that would have motivated one with no knowledge of [the inventor's] invention to make the combination in the manner claimed.") Applicant respectfully submits that the Office has been lulled into a hindsight approach to considering the obviousness of the claimed invention because of its relative simplicity, and this is improper.

The Art Teaches Away From the Claimed Invention

Finally, Applicant respectfully notes that at the time this application was filed, it was widely recognized and accepted in the medical profession that peroxide and hypochlorite were toxic and should not be administered. Attached hereto is a printout from the American Cancer Society website that includes statements regarding the use of hydrogen peroxide.[3] The American Cancer Society's position on hydrogen peroxide, which it recommends to all physicians and patients, was stated best when the Society said: "Although hydrogen peroxide is well known for its antiseptic properties, there is no evidence that it has value as a treatment for cancer or other diseases."

As the Federal Circuit has repeatedly recognized, proceeding contrary to the accepted wisdom in the art represents "strong evidence of unobviousness." *In re Hedges*, 783 F.2d at 1041, 228 U.S.P.Q. at 687; *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d at 1552, 220 U.S.P.Q. at 312 (prior art teaching that conventional polypropylene should have reduced crystallinity before stretching and should undergo slow stretching, led away from claimed process of producing porous article by expanding highly crystalline PTFE by rapid stretching); accord *In re Fine*, 837 F.2d at 1074, 5 U.S.P.Q. at 1599. And where a reference warns against rather than teaches an invention, one of skill in the art cannot be expected to combine it with another teaching. *Id.*

Contrary to the Office's position (see Office Action, page 9, lines 3-10), this line of cases does not stand for the proposition that the *only* prior art that can be considered for purposes of "teaching away" is that which is being cited by the Office. In this regard, Applicant respectfully

[3] This document was provided to the Office as an Attachment to Applicant's Response filed January 28, 2004.

refers the Office to the Supreme Court's decision in *United States v. Adams*, 383 U.S. 39 (1966), which is cited in *Gore* and *Hedges*. In that case, which related to a patent claiming a battery, the battery, when used as claimed, gave off tremendous heat, because it could not be "shut off." None of the art that the Court discussed appeared to relate to this particular issue, and it appears that none of the art which was argued to invalidate the claims mentioned it either. Yet the Court, in its conclusions relating to nonobviousness, states:

> Despite the fact that each of the elements of the Adams battery was well known in the prior art, to combine them as did Adams required that a person reasonably skilled in the prior art must ignore that (1) batteries which continued to operate on an open circuit and which heated in normal use were not practical.

(*U.S. v. Adams*, at 51-52.) The Court goes on to specifically hold that "known disadvantages in old devices which would naturally discourage the search for new inventions may be taken into account in determining obviousness." *Id.*

The Office's attention is also respectfully directed to *In Re Dow Chemical Co.*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1998). In *Dow*, the Board's decision that the claimed invention would have been obvious was based on a combination of two references. Also discussed by the Board, but expressly not relied upon, were a patent to Farmer and a publication by Bacon and Farmer. When Dow argued that the Farmer patent and Bacon and Farmer publication led away from the claimed invention, the Patent Office pointed out that it was no longer relying on those documents, and that Dow was simply creating a "straw man." But the Federal Circuit sided with Dow, stating that "[i]t is indeed pertinent that these references teach against the present invention. Evidence that supports, rather than negates, patentability must be fairly considered." *Id.* at 473. Additionally, Applicant notes that general skepticism of those in the art not amounting to teaching away is also relevant and persuasive evidence of nonobviousness. *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 726, 16 USPQ2d 1923, 1929 (Fed. Cir. 1990).

Applicant respectfully submits that the art, as represented in the cited statements above, clearly suggests that one *not* administer peroxide for treatment of cancer. The accepted wisdom among medical practitioners, i.e., people of ordinary skill, was to avoid administration of

peroxide for treatment of cancer. This is very strong evidence of the non-obviousness of the present invention, which requires, among other things, administration of at least one source of peroxide to a tumor.

The Supreme Court case of *Graham v. John Deere*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966), mandates that in considering obviousness, one must consider not only the scope and content of the prior art, but also, the level of ordinary skill in the art. In this instance, where the claim relates to methods of treating a mammal, those of ordinary skill will be medically trained. A basic tenet of medical training, be it human or veterinary, is do no harm to a patient. Thus, patient safety is a very real concern to those of ordinary skill in this art. And a medical practitioner, with the toxicity information provided by Schraufstatter et al. (of record, and discussed in prior responses) and the advisory provided by the American Cancer Society, would not be motivated to administer peroxide to a patient.

Statements regarding hypochlorite use are best summarized in the Material Safety Data Sheet for sodium hypochlorite, from the Clorox Company ("Health Hazard Data" section), a copy of which is provided as an attachment.[4] Based on the warnings in this MSDS, hypochlorite is clearly regarded as a toxic substance. Applicant respectfully submits that one of skill in the art would not have administered at least one source of hypochlorite for treatment of cancer, given that the compound was known to be so toxic.

In sum, the art clearly establishes that peroxide and hypochlorite are toxic and potentially dangerous, and the American Cancer Society, while recognizing its antiseptic qualities, actually advises *against* the administration of peroxide in treating cancer or any other disease. It is also submitted that the absence of a similar caution against the use of hypochlorite may be telling in that no one has ever even advocated its administration, so a warning is unnecessary. It is respectfully submitted that the prior art clearly teaches away from the presently claimed invention.

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[4] This document was also provided to the Office as an Attachment to Applicant's Response filed January 28, 2004.

Thus, in view of the art, there is simply no reason one would be motivated to arrive at the presently claimed invention.

B) Claims 10, 16, and 29 are not obvious over Rosen et al. (Journal of Biological Chemistry (1977) Vol. 252 (No. 14): 4803-4810) in view of the "acknowledged prior art," Vincent et al. (Cancer (1964) 17: 997-1005), Mallams et al. (Prog. Clin. Cancer (1965) Vol. 10: 137-153), and Beattie et al. (U.S. Patent No. 5,364,344).

Claim 10 is exemplary of the rejected claims. Claim 10 (including the elements of claim 1) is directed to: "A method of treating a target site in or on a mammal, comprising: administering at least one source of peroxide and at least one source of hypochlorite anion to the target site to be treated, wherein the at least one source of peroxide and at least one source of hypochlorite are from separate sources, and allowing the peroxide and hypochlorite to react to produce singlet oxygen at the target site or during administration, wherein the target site is a tumor."

The Differences Between the Claims on Appeal and the Prior Art

Appellant's claim requires *administration* of *at least one source of peroxide* and *at least one source of hypochlorite* to *allow for the generation of singlet oxygen* at the tumor. The prior art fails to teach the administration of hypochlorite and the administration of peroxide, in combination, to produce singlet oxygen at a target site.

The Cited Prior Art

Rosen et al.

Rosen et al. discusses the mammalian leukocyte's cytotoxic repertoire, which includes production of hypochlorite and peroxide, which are believed to react to form singlet oxygen. But Rosen et al. is nothing more than a study and discussion of the natural biological process. This is certainly not to minimize the importance of this truly amazing process in the body. But, for its impact on the patentability of the pending claims, Rosen et al. does nothing more than explain

that one aspect of a mammal's natural defense system involves hypochlorite, peroxide, and singlet oxygen.

Rosen et al. does not suggest that these natural components of the mammalian system can or should be administered for a therapeutic effect. There is nothing in Rosen et al. that would lead one of ordinary skill to believe that these reactants can be administered into a subject to be treated, with any expectation of therapeutic success. There is nothing in Rosen et al. that would lead to the presently claimed invention.

"Acknowledged" Prior Art

The Office cites to several paragraphs from Applicant's application that discuss photodynamic therapy in animals. Photodynamic therapy generally involves infusing a photoactive compound into a patient and allowing the compound to collect in a tumor that is to be targeted. The photoactive compound in the tumor is then irradiated with light energy to produce singlet oxygen in the target site. There are drawbacks to photodynamic therapy, which include targeting problems as well as expense. But photodynamic therapy does not involve, or relate to the use of, either peroxide or hypochlorite.

The Office cites to paragraph [017] of Applicant's specification for the proposition that the singlet oxygen made by photodynamic therapy is identical to that produced by reacting hypochlorite with peroxide. But that fact does not lead from one method of production to the other.

The Office also cites to Applicant's application (paragraph [019]) for the premise that singlet oxygen is recognized as being naturally present in humans. Applicant's discussion in this section of the application simply describes what was believed to be current hypotheses on the functioning of eukaryotic cells. These cells are believed to produce, through complicated enzymatic processes, hydrogen peroxide, hypochlorite, singlet oxygen, and other potent oxidizing compounds in connection with phagocytic activities. Indeed, this discussion is similar to that provided in Rosen et al. But again, this understanding of basic cell biology does nothing to teach or suggest Applicant's claimed invention.

Vincent et al.

The Office cites Vincent et al. for disclosing that administration of sodium hypochlorite in a single dose or as an irrigant is effective against tumor.

In response, Applicant respectfully notes that the claims require administration of not only hypochlorite, but peroxide as well. But nothing in Vincent et al. would lead to its administration along with peroxide for an anti-tumor effect. And there certainly is nothing that would give any expectation of success in a combined administration of hypochlorite and peroxide. Nothing suggests that the combined administration would provide any benefit over administration of one or the other reactant.

There is nothing in Vincent et al. that would lead to the present invention.

Mallams et al.

Mallams et al. is cited by the Office for its disclosure of intra-arterial infusion of hydrogen peroxide in cancer patients.

However, Applicant respectfully notes that Mallams et al. discloses administration of hydrogen peroxide to cancer patients to produce regional oxygenation, not for an anti-tumor effect from the peroxide. The purpose of Mallams et al.'s regional oxygenation with peroxide is to render tumor cells relatively more sensitive to radiation than non-cancer cells, i.e., to create a positive radiotherapeutic ratio. (See first paragraph of Mallams et al.) Thus, when one reads Mallams et al. in its entirety, one sees that hydrogen peroxide is used simply as an adjunct to radiation therapy in cancer patients.

For the most part, Mallams et al.'s comments relate to the improvement in radiation therapy imparted by the increased local oxygenation. Generally, Mallams et al. does not even mention the effect of hydrogen peroxide on the tumors. However, on page 149 of Mallams et al., it is stated that "[d]aily infusion of hydrogen peroxide for 1 week showed no apparent effect on

the lesion." Thus, in the only instance where Mallams et al. does comment on the direct effect of hydrogen peroxide on a cancer lesion, the effect is negative, or lacking. That is, Mallams et al. showed that, in the absence of radiation, hydrogen peroxide had no effect whatsoever on the tumor.

Applicant respectfully submits that when read in its entirety, Mallams et al. would not lead one of skill in the art to administer hydrogen peroxide for an anti-tumor effect, unless radiation therapy was also intended. In fact, Applicant submits that the negative effect, or lack of therapeutic effect, demonstrated by Mallams et al. in administering hydrogen peroxide to tumor tissue, would lead one of skill in the art away from the use of peroxide in treating tumors. That is, one of skill in the art would not choose to use a therapeutic regimen without any expectation of success.

Applicant respectfully submits that the Office's misreading of Mallams et al. is a critical flaw in its obviousness rejection. The Office cites Mallams et al. for "infusion of hydrogen peroxide in cancer patients." (Action, page 10, line 10.) And in the Action, the Office states that the "difference between the prior art and the claimed invention is that the prior art does not expressly disclose the combination of sodium hypochlorite and hydrogen peroxide to treat tumors." (Action, page 10, lines 14-16.) It is respectfully submitted that not only does the prior art not disclose the *combination* of sodium hypochlorite and hydrogen peroxide to treat tumors, it *does not disclose hydrogen peroxide* to treat tumors.

In view of these points, Applicant respectfully submits that Mallams et al. would not only not lead one of skill to the present invention, it would not be combined with other teachings.

Beattie et al.

The Office cites to Beattie et al. (U.S. Patent No. 5,364,344) for the teaching dual lumen catheters for delivering different fluids into the blood stream.

Applicant submits that the teaching of Beattie et al. no more suggests administering hypochlorite and peroxide than it does administering anything else. There is nothing in Beattie

et al. that suggests any particular compounds or substances for administration. Beattie et al. simply provides a means for administering two solutions simultaneously, if one wanted to do so. But given the art, there is no reason that one would want to administer at least one source of peroxide and at least one source of hypochlorite.

In the Office Action, the Office states that "one of ordinary skill in the art would expect that by use of a dual lumen catheter the peroxide and hypochlorite could be kept separate until the last possible moment thereby ensuring the maximum concentration of singlet oxygen possible." (Office Action, page 11, lines 3-5.) Applicant respectfully submits that none of the art relied upon by the Office suggests that peroxide and hypochlorite should be administered together for treating a mammal. Thus, it is irrelevant that one *could* use a dual lumen catheter.

The Office Applies Hindsight Analysis

The claimed invention is a method of treating a tumor by administering at least one source of peroxide and at least one source of hypochlorite anion to the tumor to be treated, wherein the at least one source of peroxide and at least one source of hypochlorite are from separate sources, and allowing the peroxide and hypochlorite to react to produce singlet oxygen at the tumor or during administration. In arguing the obviousness of the claimed invention, the Office has picked isolated teachings and combined them to arrive at the claimed invention, with nothing more than Applicant's disclosure to guide the combination. This is clearly improper.

Applicant notes that the prior art, when viewed as a whole, would not have suggested the administration of either hypochlorite or peroxide. Applicant has presented documentation to the Office that clearly warns of the toxicity of hypochlorite and peroxide. Additionally, Applicant has presented public statements from the American Cancer Society advising that while peroxide "is well known for its antiseptic properties, there is no evidence that it has value as a treatment for cancer." Indeed, one of the documents relied upon by the Office, Mallams et al., specifically states that daily infusion of hydrogen peroxide for *one week* had no effect on the lesion.

The Office has attempted to discredit these teachings by previously arguing that safety issues are not within the purview of the Patent Office, and more recently, that because these

documents were not cited against the claims, the fact that they lead away from the invention is irrelevant. Applicant respectfully submits that not only are these documents relevant to the patentability of the present claims, they support it.

The Office attributes teachings to documents that are not present in those documents. For example, Mallams et al. clearly suggests administration of hydrogen peroxide as an adjunct to radiation therapy *solely* to enrich the oxygen concentration in the locality of the tumor. Mallams et al. does not suggest hydrogen peroxide as a treatment for tumors. And, as noted above, to the extent that any direct effect was monitored, it was *negative*. Yet Mallams et al. is a key reference in the Office's rejection for obviousness.

Applicant acknowledges that hypochlorite and peroxide have been shown to react under controlled laboratory conditions to form singlet oxygen, as was shown by Foote and Wexler in 1964. However, no one has shown that those reactions could be repeated by administering these reactants to a living animal. The only support the Office has for that contention is that the mammalian leukocyte naturally produces hypochlorite and peroxide, which are believed to combine to yield singlet oxygen. But one of skill in the art would not be led to the present invention solely by this understanding of mammalian physiology.

The Office points to Applicant's discussion of photodynamic therapy, which utilizes singlet oxygen for its anti-tumor effects, in support of its obviousness rejection. But photodynamic therapy has nothing whatsoever to do with hydrogen peroxide or hypochlorite. Finally, the Office cites to a dual lumen catheter patent (Beattie et al.) for teaching the delivery of different fluids to the bloodstream. But as noted above, Beattie et al. does not suggest any element of the present invention either.

When one takes a step back and looks at the disparate teachings the Office has assembled in this rejection, one sees them for what they are: disparate teachings. There is nothing in the art that suggests the present invention, yet the Office carefully selects teachings that support its position. The Office finds reasons for combining the teachings that are not found in the prior art. This approach is based upon the hindsight of having considered Applicant's disclosure, and it is improper.

Motivation is Lacking

The motivation requirement of an obviousness rejection protects an Applicant from improper hindsight reasoning. In this instance, motivation is entirely lacking.

The Office states that the difference between the prior art and the claimed invention is that the art does not expressly suggest the combination of hypochlorite and peroxide to treat tumors.[5] (Action, page 10, lines 14-16.) The Office states that the prior art "amply suggests the same as it is known in the art to prepare solutions containing sodium hypochlorite or hydrogen peroxide for use in the treatment of tumors and that sodium hypochlorite and hydrogen peroxide react to form singlet oxygen which is effective against cancer and tumor cells." (Action, page 10, lines 16-19.) Without more, the Office concludes that one "would have been motivated to modify the prior art as above with the expectation that the combination would be effective in treating tumors." (Action, page 10, lines 20-21.) Here, the Office finds the motivation to combine the teachings in the result of the combined teachings: effective treatment of tumors.

The Office goes on to state that one "would be motivated to separately combine the peroxide and hypochlorite at the point of use so as to ensure that singlet oxygen is available for treatment of the cancer or tumor cell." (Action, page 11, lines 1-2.) Again, the Office finds motivation for its combination in the advantages that flow from the combined teachings, which were first disclosed in Applicant's specification.

If motivation could properly be found in the advantages that flowed from a combination of teachings, it would always be present. If the Patent Office was allowed to identify disparate teachings and combine them to produce an unexpectedly good result, and then find the motivation for the combination in the unexpectedly good result, then the requirement for motivation would be rendered moot. Thankfully, that is not what the motivation requirement asks.

[5] In fact, as noted above, the Office is minimizing the differences.

Motivation asks whether the teachings should be combined and, for that reason, the motivation must be found in the uncombined teachings. In this instance, there is nothing that would have led to the combination of teachings as the Office has suggested. Applicant respectfully submits that motivation is not present.

Conclusion

Appellant's claimed invention stems from the recognition that while toxic and potentially harmful if delivered alone, hypochlorite and peroxide delivered simultaneously react to form singlet oxygen. Singlet oxygen itself exhibits a powerful oxidizing effect, but is short-lived. The reaction products of sodium hypochlorite and hydrogen peroxide, thus, are short-lived singlet oxygen, sodium chloride, and water. When administered in combination, the effect is specific to the local area, with little possibility for collateral damage.

Indeed, Appellant observed that what collateral damage did occur to normal cells was quickly reversed. While the oxidative effects were permanent on abnormal cells, the normal cells in the area were able to reproduce and heal the treated area. This surprising effect could not have been predicted, and would not have been expected given the prior art teachings.

Appellant respectfully submits that the Office has failed to establish a *prima facie* case of obviousness with regard to claims 10, 16, and 29, and respectfully requests the Board reverse the outstanding rejections.

Respectfully submitted,

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APPENDIX

Appealed Claims (10, 16, and 29)

1. A method of treating a target site in or on a mammal, comprising: administering at least one source of peroxide and at least one source of hypochlorite anion to the target site to be treated, wherein the at least one source of peroxide and at least one source of hypochlorite are from separate sources, and allowing the peroxide and hypochlorite to react to produce singlet oxygen at the target site or during administration.

10. The method according to claim 1, wherein the target site is a tumor.

14. A system for treating a target site in a mammal, comprising:

a) at least one source of peroxide;

b) at least one source of hypochlorite anion, which is separate from the source of peroxide; and

c) at least one catheter having at least one lumen.

16. The system according to claim 14, wherein the target site is a tumor.

29. A method for treating tumor cells or cancer cells as a result of seeding an operative site comprising: administering as an irrigation or irrigating solution at least one source of peroxide and at least one source of hypochlorite anion.